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(54) Title: STABILIZED ANTIMICROBIAL SYSTEMS AND METHODS OF MAKING THE SAME

(57) Abstract: The present invention relates to high alcohol-containing antimicrobial compositions with improved stability of appearance and with methods of producing the same.

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STABILIZED ANTIMICROBIAL SYSTEMS AND METHODS OF MAKING
THE SAME

5

This application is related to U.S. patent applications, Serial Numbers 09/_____, entitled DEEP PENETRATING ANTIMICROBIAL COMPOSITIONS (Attorney Doc. No. JJM-510); and 09/_____, entitled NOVEL SKIN DISINFECTION PROCEDURES (Attorney Doc. No. JJM-511); and 09/_____, entitled THERAPEUTIC ANTIMICROBIAL COMPOSITIONS (Attorney Doc. No. JJM-513), all concurrently filed herewith and which are assigned to assignee of the present invention and incorporated by reference as if fully set forth herein.

15

BACKGROUND OF THE INVENTION20 1. Field of the Invention

This invention is concerned with stabilized antimicrobial systems and methods of making the same.

25 2. Related Art

The physical appearance of antimicrobial products, such as hand gels and lotions, is an important consideration of a potential user of the products.

30 While alcohol and alcohol-containing mixtures are known

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to possess bactericidal activity, such compositions are not as widely accepted for use as non-alcohol antimicrobial products because alcohol and alcohol-containing mixtures dehydrate the skin. The dehydration is caused by the denaturing and delipidizing of the skin's lipid molecules. It is appreciated in the art that lipids in the stratum corneum of the skin are important for the barrier properties of the skin.

Two ways of overcoming the dehydrating nature of alcohol-containing antimicrobial compositions are presented in commonly assigned U.S. Patent Number 5,997,893, entitled ALCOHOL BASED ANTIMICORBIAL COMPOSITIONS WITH COSMETIC APPEARANCE and co-filed patent application Serial No. _____ entitled DEEP PENETRATING ANTIMICROBIAL COMPOSITIONS (Attorney Docket JJM-510). These alcohol-containing compositions of the foregoing patent applications are effective as antimicrobial compositions that desirably possess the appearance, feel and moisturizing attributes of a hand cream and lotion. Thus, the appearance of such compositions is an important factor in overcoming the perceived drying attribute of alcohol-containing formulations. Another desirable aspect for the appearance of these formulations is that the appearance be stable, that is not change over time or separate into various phases. It is relatively easy to achieve white, lotion appearance with oil in water and/or water in oil

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type of emulsion based formulations by adding inorganic fillers or by using compounds that emulsify and offer that look to the end product. However, it is quite complex to obtain such an appearance with an excellent stability profile in a high alcohol system (i.e., 50-90 v/v% active alcohol) having 5 - 15 wt.% water, skin conditioners such as hydrophilic oil (e.g., isolene), fatty acid esters including phosphate esters such as naturally derived synthetic phospholipids (e.g., Phospholipid), humectant (e.g., glycerin), and percutaneous enhancers (propylene glycol). Some of the prototypes prepared using this combination were evaluated for the stability at elevated temperatures (40 degrees), and found to be unstable. Microscopic examination of some of these prototypes has shown separation of isolene in large quantities as an oil at the bottom of the glass vials. One solution for providing more stable high alcohol-containing antimicrobial systems and methods of forming the same are hereinafter disclosed.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1(a) depicts a microscopic view at 200X magnification of unaged Formulation 1-1.

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Fig. 1(b) depicts a microscopic view at 200X magnification of Formulation 1-1 after accelerated aging at 40 C for 5 weeks.

5 Fig. 1(c) depicts a microscopic view at 200X magnification of unaged Formulation 1-2.

10 Fig. 1(d) depicts a microscopic view at 200X magnification of Formulation 1-2 after accelerated aging at 50 C for 20 weeks.

 Fig. 1(e) depicts a microscopic view at 200X magnification of unaged Formulation 1-3.

15 Fig. 1(f) depicts a microscopic view at 200X magnification of Formulation 1-3 after accelerated aging at 50 C for 20 weeks.

20 Fig. 2(a) depicts a microscopic view at 100X magnification of Formulation 2-1 after forming a premixed paste.

25 Fig. 2(b) depicts a microscopic view at 100X magnification of unaged Formulation 2-1 after incorporating the premixed paste and forming a final antimicrobial formulation.

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Fig. 3(a) depicts a microscopic view at 200X magnification of unaged Formulation 3-1.

5 Fig. 3(b) depicts a microscopic view at 200X magnification of Formulation 3-1 after accelerated aging at 50 C for 3 weeks.

10 Fig. 3(c) depicts a microscopic view at 200X magnification of unaged Formulation 3-2.

15 Fig. 3(d) depicts a microscopic view at 200X magnification of Formulation 3-2 after accelerated aging at 50 C for 3 weeks.

SUMMARY OF THE INVENTION

20 One aspect of the present invention is based on the surprising discovery that the mere addition of a small amount of a metal oxide in a high alcohol-containing antimicrobial composition comprising at least about 50 to about 90 v/v% (approx. 40 to 70 wt./wt.% based on ethanol) of active alcohol, an effective amount of a
25 hydrophilic oil, an effective amount of a cationic antimicrobial resulted in a stable antimicrobial composition with greatly enhanced product stability in terms of appearance of alcohol-containing antimicrobial compositions. The metal oxides are preferably microfine

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(i.e., > than about 5 m²/g surface area (S.A.)) titanium dioxide and zinc oxide.

Another aspect of the invention relates to the method of forming stable antimicrobial systems containing metal oxides comprising the steps of:

(a) forming a paste of a thickener and a humectant;

(b) adding water to the paste of (a) and mixing until homogeneous;

(c) dispersing the metal oxide into a fatty acid ester, preferably a phosphate ester, by mixing in a separate vessel;

(d) adding a hydrophilic or dispersing oil to the mixture of (c) until a uniform and smooth paste is formed;

(e) adding the paste of (d) to the aqueous mixture of (b) and mixing until a thick white uniform gel is formed;

(f) dissolving a predetermined amount of a surfactant into an alcohol in a separate vessel;

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(g) slowly adding the mixture of (f) into the gel of (e) and mixing until a viscous, uniform product results; and

5 (h) mixing into (g) other desired additives, if any.

Yet another embodiment of the invention relates to forming a stable, high alcohol-containing antimicrobial composition generally comprising the steps of :
10

a) heating and hydrating a thickener;

b) cooling the composition of step (a) to form a gel;
15

c) adding an alcohol to the gel of step (b) to form a homogenous gel; and

20 d) adding any other desired additives, if any, to form a complete antimicrobial composition.

In yet a more preferred embodiment of the foregoing embodiment , the method comprises:
25

a) heating a predetermined amount of water and adding a thickener and stirring to disperse thoroughly;

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b) cooling the mixture of step (a) to room temperature to form a thick gel;

5 c) adding an alcohol slowly but with rapid stirring to the gel of step (b) to form a homogenous, clear gel;

d) dissolving a surfactant into the alcoholic gel of step(c);

10 e) dissolving the components of antimicrobials, humectants, and conditioners into the gel of step (d);

f) dissolving surfactants into the gel of step (e); and

15 g) adding any other desired ingredients, if any, to the gel of step (f).

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE
20 INVENTION

25 In one embodiment of the invention, compositions contain an amount of a metal oxide effective to provide physical stability to the composition. Typically the effective amount of metal oxides is from about 0.01 to about 1.0, preferably from about 0.05 to about 0.5, and most preferably from about 0.1 to about 0.25 weight percent of metal oxide based on individual metal oxide.

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Suitable metal oxides for use with this invention include transition and post-transition metal oxides. Most preferably the metal oxides are selected from the group consisting of zinc oxide and titanium dioxide. In the case of zinc oxide, a known skin protectant at concentrations of about 1 weight %, zinc oxide is especially preferred because of its natural, mild anti-bacterial activity with astringent and substantive skin treating properties (i.e., will bind to skin and not wash off easily thereby reducing secretions from the skin). Use of zinc oxide in non-alcohol containing compositions is known, e.g., co-pending and commonly assigned U.S. patent application, Serial No. 09/205,209, entitled SKIN CARE COMPOSITIONS CONTAINING ZINC SALTS AND RETINOIDS, discloses compositions of zinc oxide and retinoids in non-alcohol containing skin care compositions such as both water-in-oil and oil-in-water emulsions.

While not wishing to be bound by any particular theory, it is believed that the metal oxides used in this invention provide a means for the hydrophilic oil to disperse into and avoid separating out particularly after an extended period of time or under accelerated aging conditions. Thus, it is believed that the metal oxides useful in this invention should be of sufficient surface area to disperse the amount of hydrophilic oil used in

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the compositions. Good results have been achieved with Zinc Corporation of America's USP-1 grade (0.12 micron, 9 m²/g S.A.) as well as H&R's Zinc Oxide neutral H&R (2 micron, 30-70 m²/g S.A.) to have a stabilizing effect on formulations. Both of these are considered high surface area grades (microfine Zinc Oxide) as opposed to something like Zinc Corporation of America's USP-2 (0.3 micron, 3 m²/g S.A.). It is not clear what is the minimum surface area that would be required to give the enhanced stability, however the precise surface area can be easily determined by one skilled in the art and is known to depend on such variables as the precise amount of hydrophilic oil and alcohol used in the antimicrobial composition. Furthermore, one skilled in the art would appreciate that mean particle size of the metal oxide used will also correlate to the specific surface area of the material; lower particle sizes yield high surface areas. The particle size influences the opacity of the finished product.

The alcohol used with the composition of this invention is typically present in an amount ranging from about 50 to about 90 (v/v%), preferably 60 to 75 (v/v%), most preferably from about 60 to about 70 (v/v%) of the composition. The alcohols useful in the present invention include ethyl alcohol, isopropyl alcohol, n-propyl alcohol and combinations thereof. Ethyl alcohol may be used as the only alcohol or the alcohol may be a

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mixture from about 10 to 70% by volume ethyl alcohol, from about 10 to 70% by volume isopropyl alcohol, and from about 10 to 70 % by volume n-propyl alcohol.

5 Hydrophilic oil skin conditioners are oils that are miscible (i.e., do not form emulsions) with water, alcohol and hydrophobic oils. Examples of hydrophilic oils useful in this invention include isolene (C_{12} - C_{18} diglycerides - Vevy Europe), polyethylene glycol
10 derivatives of mono- and di-glycerides (e.g., Lexol ES - Inolex), silicone polyethers (such as dimethicone copolyol), organosilane quaternary ammonium compounds (e.g., Lambent Quat AD (Lambent Technologies)), and liquid fatty alcohols (e.g., oleyl alcohol). It
15 should be noted that the presence of the fatty amido group in Lambent Quat AD provides a extra degree of flexibility in formulating alcohol-surfactant systems. These components may be present in the composition if this invention in any effective amount. Typically these
20 effective amounts are from about 0.1 to about 5.0, preferably from about 0.25 to about 2.5, and most preferably from about 0.25 to about 1.5 weight percent of the composition based on each individual component.

25 Dispersing oils are those oils that may be used to carry (disperse) both compatible and incompatible ingredients. Examples of dispersing oils are hydrophobic oils that are compatible (miscible) with other types of

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hydrophobic oils but are miscible with water depending on whether the ingredient is a salt. More specific examples of dispersing oils useful in this invention include dimethicone, phenylethyl dimethicone, phosphate esters, such as cocamidopropyl phosphatidyl PG-dimonium chloride (Phospholipid PTC- Uniquema),
5 linoleamidopropyl phosphatidyl PG-dimonium chloride (Phospholipid EFA- Uniquema), coco phosphatidyl PG-dimonium chloride (Phospholipid CDM, Uniquema), and
10 borageamidopropyl phosphatidyl PG-dimonium chloride (Phospholipid GLA- Uniquema). These components may be present in the composition if this invention in any effective amount. Typically these effective amounts are from about 0.1 to about 5.0, preferably from about 0.5
15 to 2.5, and most preferably from about 1.0 to about 1.5 weight percent of the composition based on individual component.

Thickeners useful in this invention include
20 hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, PEG-4 Cellulose, xanthan gum, guar gum and derivatives thereof. These components may be present in the composition if this invention in any effective amount and mixed in any proportions.
25 Typically these effective amounts are from about 0.1 to about 2.0, preferably from about 0.2 to 1.5, and most preferably from about 0.4 to about 1.2 weight percent of the composition based on individual component.

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Humectants useful in this invention include glycerin, propylene glycol, sodium salt of pyroglutamic acid (sodium PCA), lactamide MEA (monoethanolamine) and acetamide MEA (Incromectant LAMEA- Croda). These components may be present in the composition if this invention in any effective amount. Typically these effective amounts are from about 0.1 to about 40.0, preferably from about 1.0 to 20.0, and most preferably from about 2.0 to about 15.0 weight percent of the composition.

Fatty acid esters useful in this invention include phosphate esters, emollient esters (such as isopropyl myristate and PEG-7 glyceryl cocoate (Cetiol HE- Henkel) and C₁₂-C₁₅ alcohols lactate (Ceraphyl 41- ISP). These components may be present in the composition if this invention in any effective amount. Typically these effective amounts are from about 0.1 to about 5.0, preferably from about 0.25 to about 2.5 , and most preferably from about 0.5 to about 2.0 weight percent of the composition based on individual component.

Percutaneous enhancers are compounds which enhance the absorption rate of skin conditioners and other active ingredients into, for example, the epidermis of the skin. Percutaneous enhancers useful in this invention include propylene glycol, phenoxyethanol,

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Sodium PCA, propylene carbonate, and polyester topical delivery systems such as Polyolprepolymer-2 (Penederm), Lexorez 100, Lexorez TC8, and Lexorez TL8 (Inolex). These components may be present in the composition if this invention in any effective amount. Typically these effective amounts are from about 0.1 to about 10.0, preferably from about 0.5 to 5.0, and most preferably from about 0.5 to about 2.5 weight percent of the composition based on individual component.

Surfactants useful in this invention include non-ionic, amphoteric and cationic surfactants. These components may be present in the composition if this invention in any effective amount. Typically these effective amounts are from about 1 to about 20, preferably from about 1 to 10, and most preferably from about 1 to about 5 weight percent of the composition based on individual surfactant.

Amphoteric surfactants are molecules having both positive and negative charges on the molecule. Examples of suitable amphoteric surfactants include those related or derived from betaines such as amine betaines and amido betaines. Also useful amphoteric surfactants include glycinate and/or imidazole derivatives such as coco-imidazoline mono-carboxylate and/or dicarboxylate.

Preferred amphoteric surfactants for use with this invention include hydroxysultaine, cocamidopropyl

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betaine, sodium lauriminodipropionate, and disodium lauroamphodiacetate.

5 Non-ionic surfactants are neutral molecules without any charge, and these compounds are very mild with poor foaming properties. Non-ionic compounds diminish surface tension and dissolve in water quite easily, but not in same way as common salt. They are equally soluble in oil, which is important in producing emulsions. In the
10 presence of water, they do not form simple solutions, they form complexes known as hydrates. Applications for nonionics include solubilization and for cationics, conditioning. Examples include alkyl phenol ethoxylates, fatty acid dialkanolamides, fatty acid
15 monoalkanolamides, fatty acid ethoxylates, fatty alcohol ethoxylates, fatty amine ethoxylates, substituted phenol ethoxylates, vegetable oil ethoxylates, polyalkylglycosides, sucrose esters and glyceryl laurate.

20 Generally, preferred nonionic surfactants include condensation products of one or more alkylene oxide groups with an organic hydrophobic compound, such as an aliphatic or alkyl aromatic compound. Exemplary
25 nonionic surfactants based upon polyethoxylated, polypropoxylated, or polyglyceroxylated alcohols, alkylphenols, or fatty acids.

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Further specific examples of nonionic surfactants include, for example, alkyl phenoxypolyethoxy ethanols having alkyl groups from about 7 to 18 carbon atoms and from about 6 to about 60 oxyethylene units such as, for example, heptyl phenoxypolyethoxyethanols, ethylene oxide derivatives of long chained carboxylic acids such as lauric acid, myristic acid, palmitic acid, oleic acid, and the like, or mixtures of acids such as those found in tall oil containing from about 6 to 60 oxyethylene units; ethylene oxide condensates of long-chained alcohols such as octyl, decyl, lauryl, or cetyl alcohols containing from 6 to 60 oxyethylene units; ethylene oxide condensates of long-chain or branched chain amines such as dodecyl amine, hexadecyl amine, and octadecyl amine, containing from about 6 to 60 oxyethylene units; and block copolymers of ethylene oxide sections combined with one of more hydrophobic propylene oxide sections.

Examples of cationic surfactants include, for example, lauryl pyridinium chloride, cetyldimethyl amine acetate, and alkyldimethylbenzylammonium chloride, in which the alkyl group has from 8 to 18 carbon atoms.

Other useful cationic surfactants include aliphatic fatty amines and their derivatives, homologues of aromatic amines having fatty chains - dodecylaniline, fatty amides derived from aliphatic diamines, fatty

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amides derived from disubstituted amines, quaternary ammonium compounds, amides derived from aminoalcohols and their quaternary ammonium derivatives, quaternary ammonium bases derived from fatty amides of
5 disubstituted diamines, quaternary ammonium bases of the benzimidazolines, basic compounds of pyridinium and its derivatives, quaternary ammonium compound of betaine, dimethylphenylbenzyl ammonium chloride, urethanes or basic salts of ethylene diamine, polyethylene diamines
10 and their quaternary ammonium compounds.

A particularly useful mixture of surfactants comprise from about 0.1 to about 10% active weight % of cocamidopropyl hydroxysultaine (amphoteric surfactant),
15 from about 0.1 to about 10% active weight % of polyalkylglycoside (preferably Plantaren 2000 from Henkel) or glyceryl laurate (Henkel), nonionic surfactant, and from about 0.1 to about 10 by active weight % of PPG-40 diethylmonium chloride (preferably
20 Emcol CC-42 from Witco Chem. Co.), cationic surfactant.

The mixture of amphoteric, nonionic, and cationic surfactants of this invention have been shown to be an effective surfactant system compatible with
25 high alcohol and low water systems, thereby resulting in a stable formulation. Desirably, the surfactants system contain only non-ionic and cationic surfactants.

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Antimicrobial agents useful in this invention include benzalkonium chloride, benzethonium chloride, methyl benzethonium chloride, cetylpyridinium chloride, cetrimonium chloride, cetrimonium bromide (cetrimide),
5 Cosmocil CQ (20% polyhexamethylene biguanide (PHMB)), and chlorhexidine gluconate. These components may be present in the composition if this invention in any effective amount. Typically these effective amounts (total actives) are from about 0.01 to about 5.0,
10 preferably from about 0.02 to 2.0, and most preferably from about 0.02 to about 1.0 weight percent of the composition based on individual components.

In practicing the method of preparing the metal
15 oxide containing compositions, it was found advantageous to first form a paste. Even though this method of incorporation of metal oxides proved useful in stabilizing a large number of antimicrobial solutions, some of the zinc oxide containing formulations actually
20 suffered a loss in antimicrobial efficacy as what is believed to have occurred with some of the preservatives used.

Thus, in subsequent formula preparations the zinc oxide was substituted with MEARLMAID OL pigment (a
25 pearlescent agent available for Engelhard Corporation) that has guanine, polysorbate 80 and isopropyl alcohol. Several prototypes were prepared using this compound to get the lotion look to the product. These formulations

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have exhibited discoloration and also separation of thickener (hydroxypropylcellulose) that was identified through a systematic approach by preparing base formula with water, hydroxypropylcellulose and alcohol. Due to these reasons the processing step of hydroxypropyl-cellulose has been changed to achieve a stable thick gel as described in Example 3. However, the improved process has not shown any separation but the color of the product changed to off white over period of 7 days at 40 degrees as well at 50 degrees. This discoloration was due to the amphoteric surfactant present in the formula. This was identified through preparation of series of samples with base containing hydroxypropylcellulose, alcohol, water and other ingredients.

Due to these poor stability reasons the amphoteric surfactant was dropped from the formula and prepared a series of samples with polyhexamethylene biguanide (PHMB) at three concentrations, 0.2, 0.25, and 0.3% along with other ingredients. These samples were placed at 40 and 50 degrees to establish the stability profile over 3 months time. The samples have shown excellent stability profile in appearance, pH, and viscosity, and thus formulas even without containing zinc oxide and isolene but with MEARLMAID OL have ingredients have displayed compatibility and stability as shown in Example 3.

- 20 -

The following trade name additives are useful in making formulations of this invention and the examples:

5 AMP 95 is a mixture of 2-amino-2-methyl-1-propanol, 2-(methylamino)-2-methyl-1-propanol and water in a ratio of from about 90:5:5, commercially available from Angus Chemical Company.

10 ACRITAMER® 505E. a polyvinyl carboxy polymer crosslinked with ethers of pentaerythritol, R.I.T.A available from Crystal Lake, IL.

15 AMPHOTERGE K-2, coco imidazoline dicarboxylate, available from Lonza.

ESS 9090IC is a fragrance, available from Givuan-Roure Corporation.

20 CERAPHYL 28 is a mixture of cetyl alcohol and cetyl lactate, a waxy solid commercially available for ISP Van Dyk Inc.

CERAPHYL 41 is a mixture of C₁₂ - C₁₅ alcohol lactates, available from ISP Van Dyk Inc.

25 CETIOL HE- PEG-7 glyceryl cocoate, from Henkel.

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COSMOCIL CQ is polyhexamethylene biguanide, available from Zeneca.

5 DISODIUM EDTA, U.S.P., available from Dow Chemical as Versene NA.

DOW CORNING® 580 wax is a mixture of stearoxy trimethoxy silane and stearyl alcohol.

10 DOWICIL 200, quaternium 15, Dow Chemical.

EMCOL CC42- PPG-40 dimonium chloride, or quaternium 21, available from Witco Corp. (cationic surfactant)

15 GERMABEN II is a mixture comprised of diazolidinyl urea (about 30%); methyl paraben (about 11%); propyl paraben (about 3%) and propylene glycol (about 56%), available from Sutton Laboratories.

20 GERMALL PLUS is a mixture of diazolidinyl urea (about 99%), 3-Iodo-propynylbutylcarbamate available from Sutton Laboratories.

25 INCROMECTANT LAMEA- a mixture of acetamide monoethanolamine, and lactamide monoethanolamine (Croda)

LAMBENT QUAT AD is a silicone quaternary compound (Lambent Technologies).

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LEXOREZ 100 is a saturated crosslinked hydroxy functional; polyester, comprised of glycerin, diethylene glycol, adipate crosslinked polymer, which is a viscous, hydrophobic liquid at room temperature and is dispersible in many lipids and emollients.

LEXQUAT AMG-IS, isostearamidopropyl PG dimonium chloride (Inolex Chemical Company)

10

MACKAM CBS-50G, cocamidopropyl hydroxysultaine, 50% (McIntyre) (amphoteric surfactant)

15

MEARLMAID OL contains isopropyl alcohol, guanine, and polysorbate 80 (Engelhard).

MIRATAINE CB - cocamidopropyl betaine (Rhone-Poulenc)

20

NATROSOL 250 HHR - hydroxyethylcellulose (Aqualon, Div. Of Hercules).

NISIN, a 34 amino acid polypeptide, sold as Ambicin by Applied Microbiology, Inc.

25

ORANGE ZEST B FRAGRANCE 439.454, fragrance commercially available from Firmenich.

PEG-7 Glyceryl Cocoate (see Cetiol HE)

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PEO-1 - polyethylene glycol, 21,000 M.W. INCI: PEG-5M
(R.I.T.A.)

5 PHOSPOLIPID CDM is cocophosphatidyl (PG)-dimonium
chloride, a co-synthetic, phospholipid available from
Mona Industries, Inc.

10 PHOSPHOLIPID GLA - borageamidopropyl phosphatidyl PG-
dimonium chloride (Mona).

PHOSPOLIPID PTC is cocamidopropyl phosphatidyl PG-
dimonium chloride, available form Mona Industries.

15 PLANTAREN 2000 is decyl polyglucose, available from
Henkel/Cospha. (non-ionic surfactant)

SILSOFT PEDM is phenylethyl dimethicone, available from
Witco Cooperation, Osi Specialties, Inc.

20 SEAFOAM 143.258/GGE FRAGRANCE, available from Firmenich,
Inc.

25 TOCOPHEROL (dl-alpha-tocopherol), Vitamin E, available
from Roche Vitamins and Fine Chemicals.

TRICLOSAN - 2, 4, 4'-trichloro-2-hydroxydiphenyl ether
available from Ciba Specialty Chemical Corp.)

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ULTREZ® 10 a carbomer polymer, available from BF
Goodrich, Cleveland Ohio, and disclosed in US patent 5,
004,598, the contents of which are incorporated by
reference in its entirety.

VARISOFT 300 is a quaternary ammonium chloride,
cetrimonium chloride (Witco Corp.).
VAROX 270 lauramine oxide, 30% active of 70% C₁₂,
available from Witco.

ZINC OXIDE is USP-1 grade microfine zinc oxide having
approximately a 0.12 micron particle size and
approximately 9 m²/g S.A. (Zinc Corp. of America).

EXAMPLE 1

Table 1 represents three(3) formulations of varying
compositions which comparatively indicate the inventive
aspects of this invention relating to the inclusion of
zinc oxide as stabilizing material.

TABLE 1*

INGREDIENTS	Formulation 1-1	Formulation 1-2	Formulation 1-3
Deionized Water	12.74	26.79	26.84
Ethanol (200 Proof)	62.25 (70%V/V)	47.10 (55.0 V/V%)	47.10 (55.0 V/V%)
Glycerin	5.0	5.00	5.00
Propylene Glycol	5.0	5.00	5.00
Plantaren 2000	3.6	3.60	3.60
Mackam CBS-50G	2.4	2.40	2.40
Benzethonium Chloride	0.1	--	--
Benzalkonium Chloride (50%)	0.2	2.00	2.00
Phospholipid CDM	1.5	1.50	1.50
PPG-40 Diethylmonium Chloride (Emcol CC-42)	1.2	1.20	1.20
Hydroxypropylcellulose HXF Grade	1.0	1.10	1.10

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Phenoxyethanol	1.0	1.00	1.00
Glyceryl Laurate	1.00	1.00	1.00
Cetrimonium Chloride (29%- Varisoft 300)	0.86	0.86	0.86
Isolene	1.0	0.50	0.50
Lambent Quat AD	0.50	0.50	0.50
Fragrance (Seafoam GGE)	--	0.15	0.15
Fragrance (Orange Zest B)	0.15	--	--
Mearlmaid OL	0.1	0.15	
Cetylpyridinium Chloride	0.1	0.10	0.10
Silsoft PEDM	0.05	0.05	0.05
Dowicil 200	0.25	--	--
Zinc Oxide (USP-1 microfine)	--	--	0.10

* All amounts in wt.% unless otherwise shown.

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Both zero time and accelerated aged time microscopic (200X) observations were made for the foregoing formulations.

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Examination of Formulation 1-1 at zero aging time and accelerated aging at 40°C for five weeks revealed that the opaque appearance of the composition was adversely affected. Visually the appearance of the aged material was less white than the appearance of unaged material. Furthermore, 200X magnification using a ZEISS, model no. Axioskop 50, microscope revealed that the aged product contained enlarged oil droplets of varying sizes (see Fig. 1(b)) whereas the unaged product contained oil droplets of more uniform size (see Fig. 1(a)). Since the opaque, lotion-like appearance of the composition is attributed to the dispersed hydrophilic oil, isolene, and the pearlescent pigment, the enlarged and varied droplets of the aged composition suggested that the aging caused an instability in the oil phase.

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Further aging of Formulation 1-1 for five weeks at 40°C showed a visibly separated bottom layer of isolene.

Formulation 1-2, which contained a lower level of isolene (0.5 wt.% vs. 1.0 wt.% compared with Formulation 1-1), but no zinc oxide, also proved not to provide a stable formulation. While Fig. 1(c) shows somewhat of an improvement at zero time (due to the decrease in the amount of isolene used), after accelerated aging at 50 C for 20 weeks, Fig. 1 (d) shows a marked degradation in the homogeneity of the formulation. Thus, Formulation 1-2 did not form a stable formulation.

However, Formulation 1-3 which contained isolene at 0.5 wt.% and zinc oxide at 0.1 wt.% provided a stable composition at both zero time and accelerated again at 50 °C for 20 weeks as noted by Formulation 1-2's homogeneous appearance as seen in Figs. 1(e) and 1(f).

EXAMPLE 2

This example demonstrates a preferred method of making the compositions of this invention which contain hydrophilic oils and metal oxides. Formulation 2-1 was made according to the steps outlined below:

TABLE 2*

Formulation 2-1	SUPPLIER	WL %
DEIONIZED WATER	J&J MED.	26.24
Ethanol (200 Proof)	Aaper	21.90
n-propyl alcohol	Aldrich	26.8
Glycerin	Henkel	5.0
Propylene Glycol	Dow	5.0

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Plantaren 2000	Henkel	3.60
Mackam CBS-50G	McIntyre	2.40
Benzethonium Chloride	Lonza	1.0
Phospholipid CDM	Mona	1.50
PPG-40 Diethylmonium Chloride (Emcol CC-42)	Witco	1.20
Hydroxypropylcellulose HXF Grade	Aqualon	1.10
Phenoxyethanol	Dow	1.00
Glyceryl Laurate	Henkel	1.00
Cetrimonium Chloride (29%- Varisoft 300)	Witco	0.86
Isolene	Vevy	0.50
Lambent Quat AD	Lambent	0.50
Fragrance (Seafoam GGE)	Firmenich	0.15
Cetylpyridinium Chloride	Zeeland	0.10
Zinc Oxide (USP-1, microfine)	ZCA	0.10
Silsoft PEDM	Witco	0.05

* All amounts in wt.% unless otherwise shown.

Formulation 2-1 was made according to the following steps:

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1. Make a uniform paste from the glycerin and hydroxypropylcellulose.
2. Add the total amount of water to the mixture in step one at 60 C. Stir until well-distributed.
3. Make a paste of zinc oxide and one-third of the total phospholipid CDM until uniform. Add the isolene and Silsoft PEDM. Mix until a uniform paste.
4. Add the paste of step 3 into the heated mixture in step 2. Cool the mixture to room temperature, mixing to form a uniform white gel (see, Fig. 2(a)).
5. Dissolve the glyceryl laurate in the mixture of alcohols.

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6. Add the alcohol-mixture of step 5 to the gel of step 4 slowly with thorough mixing, to form a uniform gel.
7. Added remaining antimicrobials, emollients, and surfactants to form the final product.

The final product of step 7 is a smooth, uniform white gel (see Fig. 2(b)).

EXAMPLE 3

This example demonstrates a preferred method of making the compositions which do not contain any metal oxides. The formulations of Table 3 were made according to the steps outlined below:

TABLE 3*

COMPONENT	SUPPLIER	Formulation 3-1	Formulation 3-2
DEIONIZED WATER	J&J MED.	15.83	10.08
Ethanol (200 Proof)	Aaper	62.0	62.5
Propylene Glycol	Dow	10.0	10.0
Glycerin	Henkel	—	5.0
Glyceryl Laurate	Henkel	2.50	2.50
Cetrimonium Chloride (29%- Varisoft 300)	Witco	2.50	2.50
Cosmocil CQ (20% PHMB)	Avecia	1.25	1.50
Phospholipid CDM	Mona	1.50	1.50
PPG-40 Diethylmonium Chloride (Emcol CC-42)	Witco	1.50	1.50
Phenoxyethanol	Dow	1.00	1.00
Hydroxypropylcellulose HXF Grade	Aqualon	0.80	0.80
Lambent Quat AD	Lambent	0.50	0.50
Benzalkonium Chloride (50%)	Lonza	0.20	0.20
Fragrance (Seafoam GGE)	Firmenich	0.15	0.15
Benzethonium Chloride	Lonza	0.1	0.1
Mearimaide OL	Engelhard	0.1	0.1
Silsoft PEDM	Witco	0.075	0.075

* All amounts in wt.% unless otherwise shown.

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The formulations of Table 3 was made according to the following steps:

- 5 1. Heat total amount of added deionized water to 60 C. Add the thickener (hydroxypropylcellulose) and stir to disperse thoroughly.
2. Cool mixture to room temperature, forming a thick gel.
- 10 3. With rapid stirring, add the alcohol slowly, making sure the particles of aqueous gel are thoroughly homogenized into the alcohol, forming a very clear gel.
4. The glyceryl laurate is dissolved in the alcoholic gel.
- 15 5. The antimicrobials, humectants, and conditioners are dissolved in the gel.
6. The surfactants are dissolved in the gel.
7. All remaining ingredients (opacifiers, i.e.,
- 20 MEARLMAID OL) are introduced with high speed mixing to form the final product.

Microscopic examination of the final Formulations 3-1 and 3-2 (Figs. 3(a) and 3(c) (zero time, respectively) and Figs. 3(b) and 3(d) (accelerated aging of 50 C for 4 and 50 C for 3 weeks, respectively)) indicated stable high alcohol antimicrobial formulations were achieved. Please note that all these Figs. (i.e., Figs. 3(a) to 3(d)), the small droplet particles are believed to be the

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dispersing oil of SILSOFT PEDM while the larger, fish scale-like particles are believed to be the MEARLMAID OL pigment which gives the formulation its pearlescent, lotion-like appearance. The important feature to note in these Figs. is that formulations remained stable, i.e., no noticeable changes in dispersing oil droplet size or number for the aged samples. Furthermore, none of the foregoing unaged or aged formulations showed any visible signs of phase separation and maintained a stable, unchanged color.

It should be understood that the foregoing disclosure and description of the present invention are illustrative and explanatory thereof and various changes in the size, shape and materials as well as in the description of the preferred embodiment may be made without departing from the spirit of the invention.

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What is claimed is:

1. An antimicrobial composition comprising at least about
50 v/v% alcohol, an effective amount of a hydrophilic
oil, an effective amount of a cationic antimicrobial
compound, and an effective amount of a metal oxide.

2. The composition of claim 1, wherein the hydrophilic
oil is isolene (C₁₂-C₁₈ diglycerides), polyethylene
glycol derivatives of mono and di-glycerides,
silicone polyethers, dimethicone copolyol,
organosilane quaternary ammonium compounds, liquid
fatty alcohols, and oleyl alcohol, and mixtures
thereof.

3. The composition of claim 2, wherein the metal oxide is
a transition or post-transition metal oxide.

4. The composition of claim 3 wherein the metal oxide is
selected from the group consisting of titanium dioxide
and zinc oxide, and mixtures thereof.

5. The composition of claim 4, where in the surface area
of the metal oxide is at least 5 m²/g.

6. The antimicrobial composition of claim 5 wherein the
alcohol is selected from the group of ethyl alcohol,
isopropyl alcohol, and n-propyl alcohol, and mixtures

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7. The composition of claim 6, wherein the cationic antimicrobial is selected from the group consisting of benzalkonium chloride, methyl benzethonium chloride, benzethonium chloride, cetyl pyridinium chloride, polyhexamethylene biguanide, and chlorhexidine gluconate, and mixtures thereof.

8. The composition of claim 7, wherein the composition further comprises effective amounts of humectants, phospholipids, and surfactants.

9. The composition of claim 1, wherein the alcohol comprises from about 50 to about 90 (v/v) percent alcohol, from about 0.1 to 5.0 weight percent of a hydrophilic oil, from about 0.01 to about 5.0 weight percent of a cationic antimicrobial compound, and from about 0.01 to about 1.0 weight percent of a metal oxide.

10. The composition of claim 9, comprising from about 65 to about 75 (v/v) percent ethanol, from about 0.25 to about 2.5 weight percent isolene ($C_{12} - C_{18}$ diglyceride), from about 0.02 to about 5.0 weight percent each of a cationic antimicrobial compounds selected from the group consisting of methyl benzethonium chloride, benzethonium chloride, benzalkonium chloride, cetrimonium chloride,

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cetylpyridium chloride, polyhexamethylene biguanide, and chlorhexidine gluconate, and mixtures thereof, and from about 0.05 to about 0.5 weight percent of zinc oxide.

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11. The composition of claim 10, further comprising from about 0.1 to about 2.0 weight percent of a thickener selected from the group consisting of hydroxypropylcellulose, hydroxyethylcellulose,
10 hydroxypropylmethylcellulose, PEG-4 cellulose xanthan gum, guar gum and derivatives thereof, and mixtures thereof.

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12. The composition of claim 11, further comprising from about 0.1 to about 5.0 weight percent of a dispersing oil selected from the group consisting of dimethicone, phenylethyl dimethicone, and phosphate esters and mixtures thereof.

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13. The composition of claim 12 wherein the phosphate ester is selected from the group consisting of cocamidopropyl phosphatidyl PG-dimonium chloride, linoleamidopropyl phosphatidyl PG-dimonium chloride, coco phosphatidyl PG-dimonium chloride, and
25 borageamidopropyl phosphatidyl PG-dimonium chloride, and mixtures thereof.

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14. The composition of claim 13, further comprising from about 0.1 to about 40.0 weight percent of a humectant selected from the group consisting of glycerin, propylene glycol, sodium salts of pyroglutamic acid (sodium PCA), lactamide MEA (monoethanolamine), and acetamide MEA, and mixtures thereof.
15. The composition of claim 14, further comprising from about 0.1 to about 5.0 weight percent of a fatty acid ester wherein the fatty acid ester is an emollient esters.
16. The composition of claim 15 wherein the emollient esters are selected from the group consisting of isopropyl myristate, PEG-7 glyceryl cocoate, and C₁₂-C₁₅ alcohols lactate, and mixtures thereof.
17. The composition of claim 16, further comprising from about 0.1 to about 10.0 weight percent of a percutaneous enhancer selected from the group consisting of propylene glycol, phenoxyethanol, Sodium PCA (pyroglutamic acid), propylene carbonate, and polyester topical delivery systems, and mixtures thereof.
18. The composition of claim 17, further comprising from about 1.0 to about 25.0 weight percent of a

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surfactant system selected from the group consisting of non-ionic, amphoteric, and cationic surfactants and mixtures thereof.

5 19. The composition of claim 18 wherein the nonionic surfactants are selected from the group consisting of alkyl phenol ethoxylates, fatty acid dialkanolamides, fatty acid monoalkanolamides, fatty acid ethoxylates, fatty alcohol ethoxylates, fatty amine ethoxylates,
10 substituted phenol ethoxylates, vegetable oil ethoxylates, polyalkylglycosides, sucrose esters and glyceryl laurate; the amphoteric surfactants are selected from the group consisting of hydroxysultaine, cocamidopropyl betaine, and sodium
15 lauriminodipropionate, and disodium lauroamphodiacetate ; and the cationic surfactants are selected from the group consisting of lauryl pyridinium chloride, cetyldimethyl amine acetate, PPG-40 diethylmonium chloride, and
20 alkyldimethylbenzylammonium chloride, in which the alkyl group has from 8 to 18 carbon atoms .

20. The composition of claim 19 wherein the surfactant system consists of nonionic and cationic surfactants.

25 21. The composition of claim 20 further comprising a pearlescent pigment.

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22. The composition of claim 21 wherein the pigment comprises isopropyl alcohol, guanine and polysorbate 80.

5 23. A method of forming stable antimicrobial systems containing metal oxides comprising the steps of:

 (a) forming a paste of a thickener and a humectant;

10

 (b) adding water to the paste of (a) and mixing until homogeneous;

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 (c) dispersing a metal oxide into a fatty acid ester by mixing in a separate vessel;

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 (d) adding a hydrophilic or dispersing oil to the mixture of (c) until a uniform and smooth paste is formed;

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 (e) adding the paste of (d) to the aqueous mixture of (b) and mixing until a thick white uniform gel is formed;

 (f) dissolving a predetermined amount of a surfactant into an alcohol in a separate vessel;

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- (g) slowly adding the mixture of (f) into the gel of (e) and mixing until a viscous, uniform product results; and
- (h) mixing into (g) other desired additives.

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24. A method for forming an antimicrobial composition comprising the steps of :

a) heating and hydrating a thickener;

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b) cooling the composition of step (a) to form a gel;

c) adding an alcohol to the gel of step (b) to form a homogenous gel; and

15

d) adding any other desired additives to form a complete antimicrobial composition.

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25. A method of forming an antimicrobial composition comprising the steps of:

a) heating a predetermined amount of water and adding a thickener and stirring to disperse thoroughly;

25

b) cooling the mixture of step (a) to room temperature to form a thick gel;

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c) adding an alcohol slowly but with rapid stirring to the gel of step (b) to form a homogenous, clear gel;

5 d) dissolving a surfactant into the alcoholic gel of step (c);

e) dissolving the components of antimicrobials, humectants, and conditioners into the gel of step (d);

10 f) dissolving surfactants into the gel of step (e); and

g) adding any other desired ingredients to the gel of step (f).

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FIG. 1a



FIG. 1b

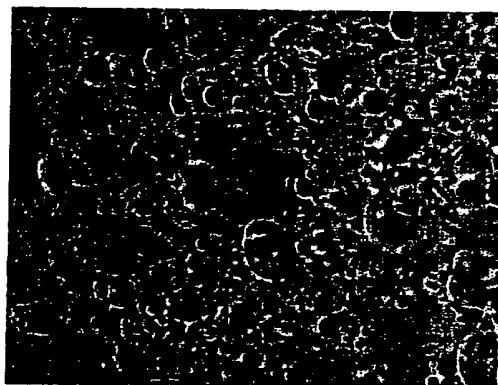
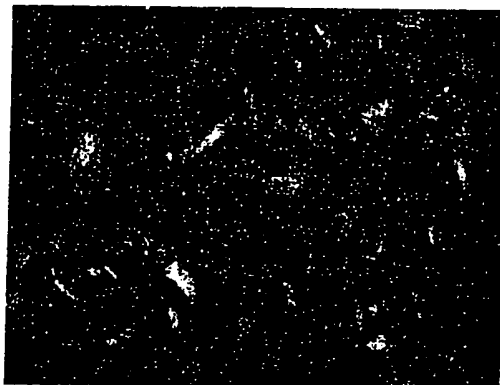


FIG. 1c



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FIG. 1d

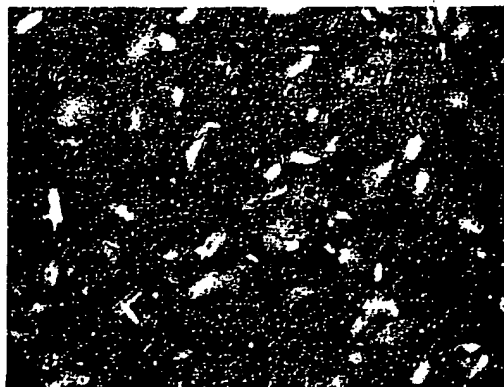


FIG. 1e

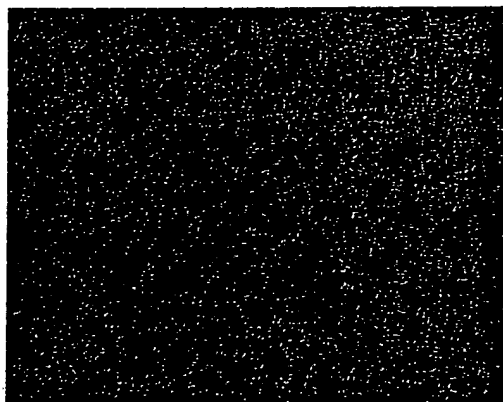
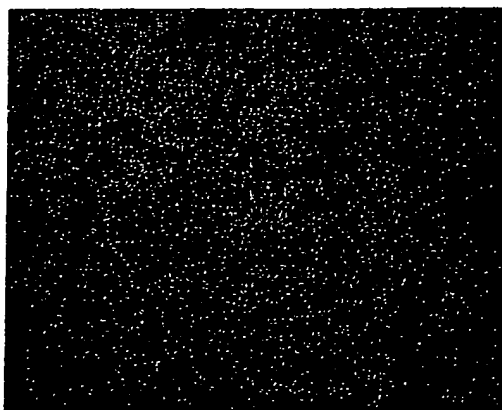


FIG. 1f



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FIG. 2a

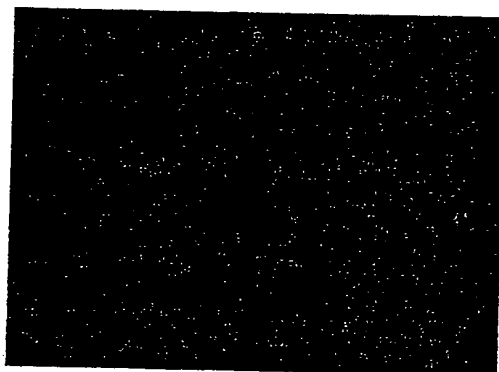
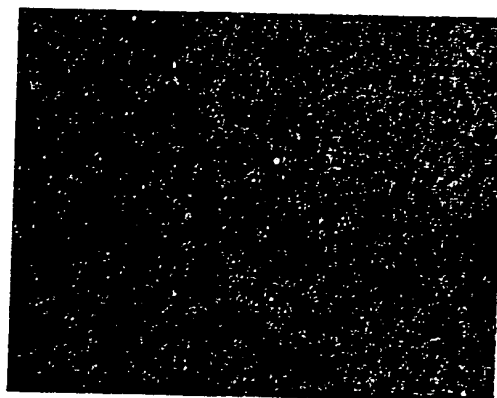


FIG. 2b



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FIG. 3a

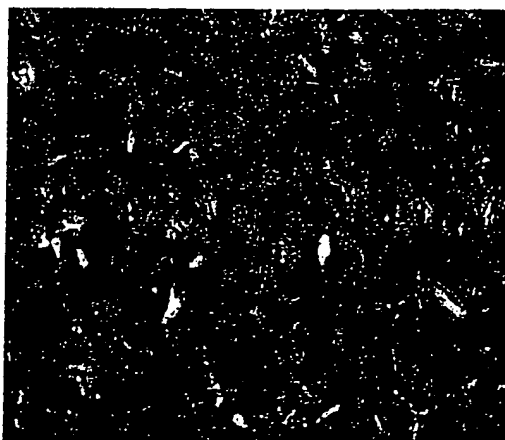
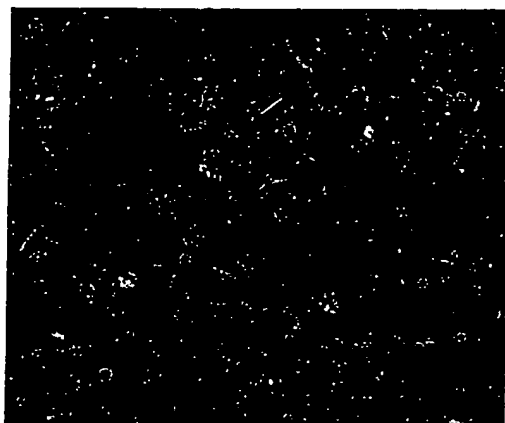


FIG. 3b



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FIG. 3c

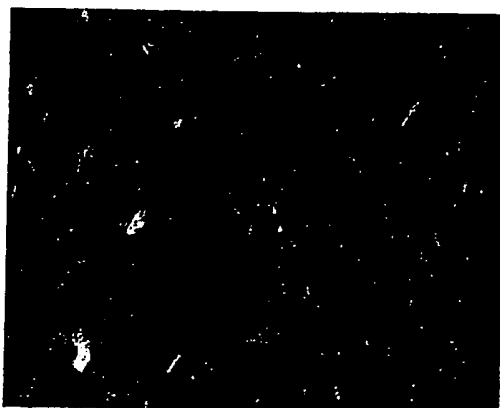


FIG. 3d



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/34008

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K7/40 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 00667 A (MINNESOTA MINING & MFG) 9 January 1997 (1997-01-09) page 35, line 29; claims 1,3,6,8; examples 23,24	1-4,6-9
X	WO 99 59540 A (GAAAF THALIE PAULINA DE ;GALLEY EDWARD (GB); BOOTS CO PLC (GB); BU) 25 November 1999 (1999-11-25) claims 1,2; example 18	1,3-6
A	EP 0 769 291 A (BEIERSDORF AG) 23 April 1997 (1997-04-23) page 3, line 35-43; claim 1	1-6
A	EP 0 640 285 A (SCHUELKE & MAYR GMBH) 1 March 1995 (1995-03-01) claims	1,2,6,7

☐ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

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05/04/2001

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/34008

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9700667 A	09-01-1997	AU 715827 B AU 6044596 A CA 2224798 A EP 0833605 A JP 11508252 T US 5951993 A	10-02-2000 22-01-1997 09-01-1997 08-04-1998 21-07-1999 14-09-1999
WO 9959540 A	25-11-1999	AU 4367699 A EP 1079799 A	06-12-1999 07-03-2001
EP 0769291 A	23-04-1997	DE 19538555 A	24-04-1997
EP 0640285 A	01-03-1995	DE 4329517 A AU 669450 B AU 7154694 A CA 2130284 A,C DE 59406395 D ES 2118317 T	02-03-1995 06-06-1996 09-03-1995 01-03-1995 13-08-1998 16-09-1998

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